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RESEARCH REPORT

Phase II trial of CV301 vaccine combined with atezolizumab in advanced urothelial carcinoma

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Abstract

CV301 comprises recombinant poxviruses, Modified Vaccinia Ankara (MVA) and Fowlpox (FPV), encoding CEA, MUC-1, and co-stimulatory Molecules (TRICOM) ICAM-1, LFA-3, and B7-1. MVA-BN-CV301 is used for priming and FPV-CV301 is used for boosting. A Phase 2, single-arm trial was designed to evaluate CV301 plus atezolizumab as first-line treatment for cisplatin-ineligible advanced urothelial carcinoma (aUC) (Cohort 1) or progressing after platinum chemotherapy (Cohort 2). MVA-CV301 was given subcutaneously (SC) on Days 1 and 22 and FPV-CV301 SC from day 43 every 21 days for 4 doses, then tapered gradually over up to 2 years. Atezolizumab 1200 mg IV was given every 21 days. The primary endpoint was objective response rate (ORR). Overall, 43 evaluable patients received therapy: 19 in Cohort 1; 24 in Cohort 2; nine experienced ≥ Grade 3 therapy-related adverse events. In Cohort 1, one had partial response (PR) (ORR 5.3%, 90% CI 0.3, 22.6). In Cohort 2, 1 complete response and 1 PR were noted (ORR 8.3%, 90% CI 1.5, 24.0). The trial was halted for futility. Patients exhibiting benefit demonstrated T-cell response to CEA and MUC-1. The trial illustrates the challenges in the development of vaccines, which should be guided by robust preclinical data.

Keywords CV301 · Poxvirus · Vaccine · Atezolizumab · Urothelial carcinoma · Bladder cancer

Background

Advanced urothelial carcinoma (aUC) is generally incurable with modest survival benefit provided by first-line platinum-based chemotherapy [1, 2]]. PD1/L1 inhibitors have an established role in the post-platinum and first-line cisplatin- or platinum-ineligible settings [3, 4]]. However, durable responses with PD1/L1 inhibitors are observed in only 15–25% of patients. Other novel agents provide benefit but are not curative. Hence, new and safe therapeutic approaches are needed.

Poxviruses have been used to deliver antigens in vaccines, given their ability to carry large antigens, promote antigen presentation, prime T cells and activate adaptive immunity by triggering Toll-like receptor (TLR)-dependent and -independent cytokines. CV301 comprises two recombinant non-replicative poxviruses, Modified Vaccinia Ankara (MVA) and Fowlpox (FPV), encoding the human transgenes for CEA, MUC-1, and a Triad of Co-stimulatory Molecules (TRICOM: ICAM-1, LFA-3, and B7-1). MVA-CV301

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is used for priming and FPV-CV301 is used for boosting MUC1- and CEA-specific immune responses.

CV301 has demonstrated an acceptable safety profile as monotherapy or in combination with PD1 inhibitors in phase I clinical trials [5], 6, 7]. The expression of CEA in bladder cancer has been reported in 41% to 90% of tumors [8–10]] and MUC-1 expression in 55% to 100% [11, 12]. Therefore, we hypothesized that the combination of CV301 and atezolizumab would be safe and effective in patients who are cisplatin-ineligible or have platinum-refractory aUC.

Methods

Trial design and patients

This was a Phase II, non-randomized, multi-institutional clinical trial designed to study the combination of CV301 with atezolizumab in the treatment of aUC. Two cohorts were eligible: 1) patients untreated for aUC, who were cisplatin-ineligible due to ≥ 1 of the following conditions: ECOG-PS-2, creatinine clearance 30 to < 60 ml/min, hearing loss or peripheral neuropathy > grade 1, and 2) patients with aUC progression after first-line platinum-based chemotherapy. The eligible population included patients ≥ 18 years with aUC consisting of locally advanced/unresectable or metastatic UC, ECOG-PS 0–2, measurable disease by RECIST 1.1 criteria and dominant urothelial carcinoma. Patients were not allowed to have prior treatment with CD137 agonists or cytotoxic T lymphocyte-associated (CTLA)-4 and PD1/L1 inhibitors.

Treatment

MVA-BN-CV301 was given subcutaneously (SC) on Days 1 and 22 and FPV-CV301 SC from day 43 every 21 days for 4 doses, then every 6 weeks until 6 months, then every 12 weeks until 2 years in the absence of progressive disease, intolerable toxicities or patient decision to discontinue. The dose of MVA-BN-CV301 was nominal titer 1.6 × 10E9 infectious units (Inf.U) given as four 0.5 mL injections. A dose of FPV-CV301 consisted of nominal titer of 1 × 10E9 Inf.U in a single 0.5 mL injection. Atezolizumab 1200 mg was given intravenously every 21 days.

Statistical assumptions

The trial was performed using an optimal two-stage design within each cohort using objective response rate (ORR) by RECIST 1.1. The secondary endpoints were overall survival (OS), progression-free survival (PFS), duration of response (DOR), adverse events (AEs) and antigen-specific T-cell responses to CEA and MUC-1 by ELISPOT. Using 1-sided α 2.5%, a 2-stage design with overall 33 and 35 patients, respectively, would achieve ≥ 70% power if the true ORR for Cohort 1 was 43% and Cohort 2 was 33%. Cohort 1 was to enroll 14 patients in stage 1 and if objective response was not achieved in ≥ 4 patients, the cohort would be stopped for futility. Cohort 2 was to enroll 13 patients in stage 1, and if objective response was not achieved in ≥ 3 patients, the cohort would be stopped for futility. The Data and Safety Monitoring Board reviewed data on an ongoing basis. The trial was approved by the institutional review boards.

Results

Patient characteristics

Overall, 43 evaluable patients received therapy since the trial was halted for futility: 19 in Cohort 1; 24 in Cohort 2 (Supplementary Table 1). Additional subjects continued to enroll in each cohort during stage 1 when awaiting data to determine whether the criteria were met for futility in the first 14 subjects in Cohort 1 or the first 13 subjects in Cohort 2, leading to accrual beyond the required targets. In Cohort 1 with 84% men and median age 78 years (range: 71–94 years), ECOG-PS was 0 in 53% and the primary tumor site was bladder for 68% of patients (Supplementary Tables 2 and 3). Most common sites of metastasis were lungs (57.9%) and lymph nodes (52.6%). In Cohort 2 with 79% men and median age 71 years (range: 43–85 years), ECOG-PS was 0 in 50% and the primary tumor site was bladder for 88% of patients. Most common sites of metastasis were lymph nodes (70.8%) and lungs (41.7%). PD-L1 expression status was optional and was not possible to assess in 16 (84%) and 20 (83.3%) patients in Cohorts 1 and 2, respectively.

Efficacy

In Cohort 1, one patient had partial response (PR), for ORR 5.3% (90% CI 0.3, 22.6) and five (26.3%, 90% CI 11.0, 47.6) had stable disease (SD) as best response (Table 1). In Cohort 2, one patient had complete response (CR) and one had PR, for ORR 8.3% (90% CI 1.5, 24.0) and 3 (12.5%, 90% CI 3.5, 29.2) had SD as best response. In Cohort 1, the patient with PR had duration of response (DOR) of 13.5 months (Fig. 1A). In Cohort 2, the 2 patients with CR and PR had DOR of 21.3 and 12.5 months, respectively (Fig. 1B). Median PFS (Fig. 2) and OS (Fig. 3) in Cohort 1 were 2.0 (90% CI 1.68, 2.10) and 13.8 (90% CI 2.37, NE) months, and in Cohort 2 were 1.95 (90% CI 1.87, 2.07) and 8.13 (90% CI 4.30, NE) months, respectively (Fig. 3). The 18-month PFS and OS in Cohort 1 were 5.3% and 15.8%, respectively; the 18-month PFS and OS in Cohort 2 were 4.2% and 29.2%,

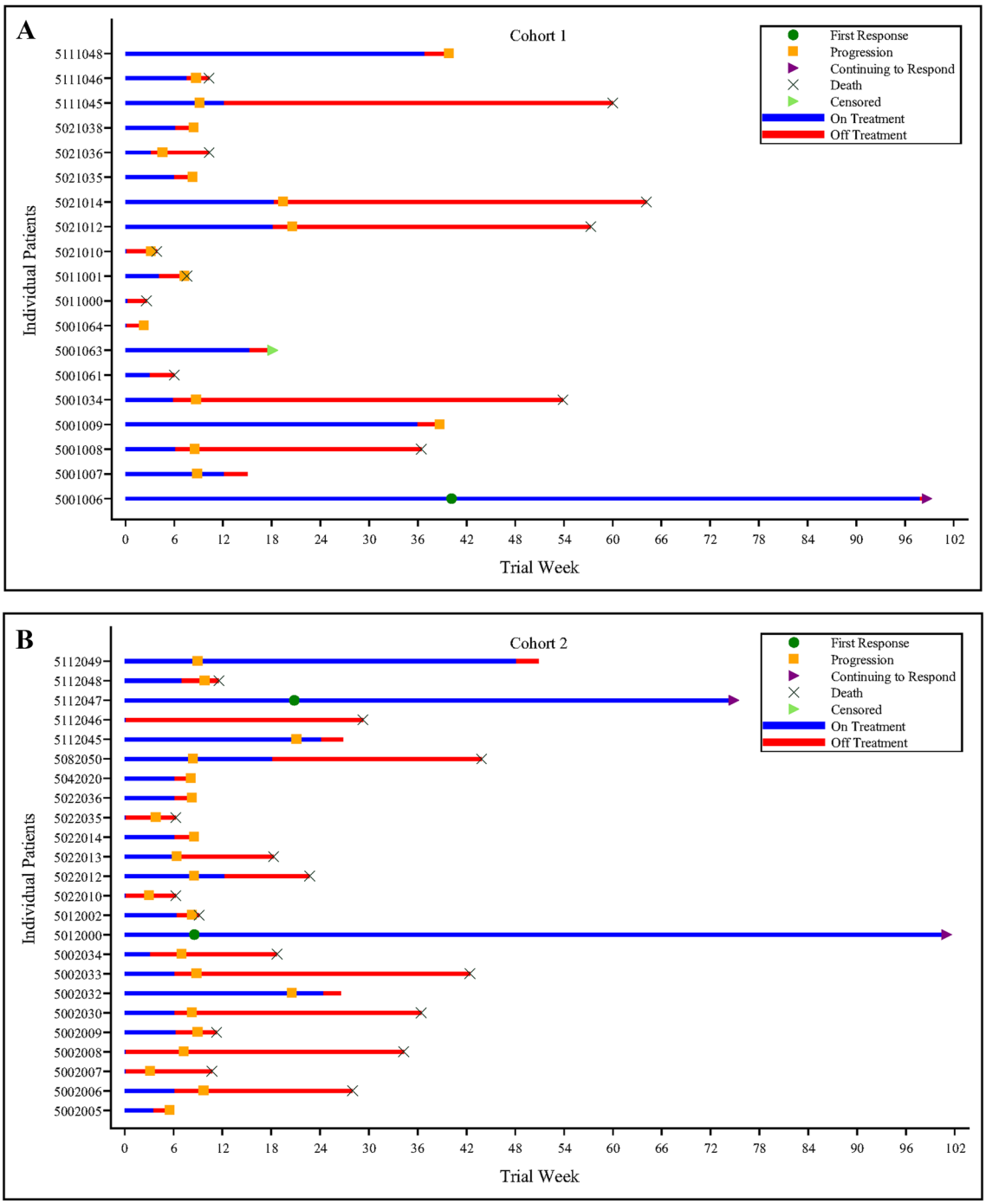

Fig. 1 Individual Subject Response by Trial Week Legend: **A** depicts Cohort 1 = First-line treatment, ineligible for cisplatin-containing chemotherapy. **B** depicts Cohort 2 = Second-line treatment, previously treated with standard first-line cisplatin-based chemotherapy. The figure includes all subjects who received any amount of trial vaccine, whether MVA-BN-CV301 alone or followed by FPV-CV301. Subjects were censored at the last tumor assessment when neither objective response nor tumor progression/death occurred during the study. Abbreviations: Inf.U = infectious units; PD-1/L1 = programmed death 1/programmed death ligand 1

respectively. Since the study was terminated early and the subjects were followed through until death or termination of study, median follow-up for both cohorts was the same as median OS, 13.8 months in Cohort 1 and 8.13 months in Cohort 2.

In Cohort 1, 84% of patients received both prime doses of MVA-BN-CV301, and the median number of boost

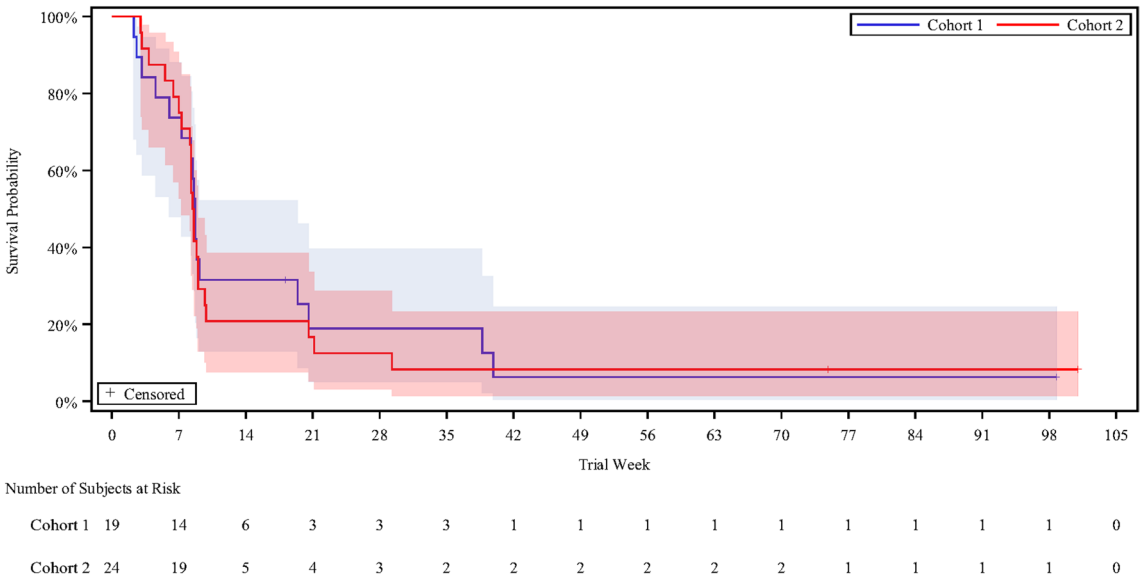

Fig. 2 Kaplan–Meier Plot of Progression-Free Survival Abbreviations: Inf.U = infectious units; PD-1/L1 = programmed death 1/programmed death ligand 1; RECIST = Response Evaluation Criteria In Solid Tumors. Legend: Cohort 1 = First-line treatment, ineligible for cisplatin-containing chemotherapy. Cohort 2 = Second-line treatment, previously treated with standard first-line cisplatin-based chemotherapy, PD-1/L1 inhibitor naïve. The figure includes all subjects who received any amount of trial vaccine, whether MVA-BN-CV301 alone or followed by FPV–CV301. Kaplan–Meier method estimates were used to create the figure. Time to progression included progression per Investigator assessment using modified RECIST v1.1 or death due to any cause. Subjects were censored at the last radiographic scan, which indicated no progression if the endpoint had not occurred for the subject

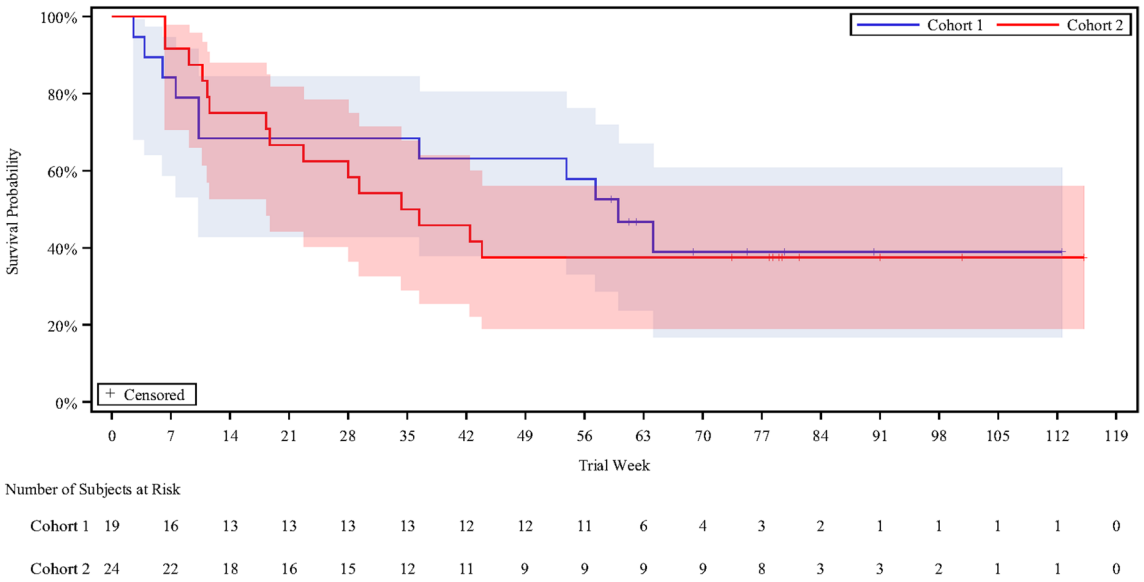

Fig. 3 Kaplan–Meier Plot of Overall Survival Abbreviations: Inf.U = infectious units; PD-1/L1 = programmed death 1/programmed death ligand 1; RECIST = Response Evaluation Criteria In Solid Tumors. Legend: Cohort 1 = First-line treatment, ineligible for cisplatin-containing chemotherapy. Cohort 2 = Second-line treatment, previously treated with standard first-line cisplatin-based chemotherapy, PD-1/L1 inhibitor naïve. The figure includes all subjects who received any amount of trial vaccine, whether MVA-BN-CV301 alone or followed by FPV-CV301. Kaplan–Meier method estimates were used to create the figure. Overall survival included death due to any cause. Subjects were censored at the end of the follow-up, early termination, or the last attended trial visit if subjects were ongoing with no survival endpoint

Table 1 Best Overall Response using RECIST v1.1

Best Overall Response per RECIST v1.1[b]	MVA-BN-CV301/FPV-CV301 and Atezolizumab			
	Cohort 1 ($N = 19$)		Cohort 2 ($N = 24$)	
	Response (Rate), *n* (%)	90% CI[a]	Response (Rate), *n* (%)	90% CI[a]
Subjects with Assessment	19		24	
Objective Response (CR or PR)	1 (5.3)	[0.3, 22.6]	2 (8.3)	[1.5, 24.0]
Complete Response (CR)	0 (0.0)	[0.0, 14.6]	1 (4.2)	[0.2, 18.3]
Partial Response (PR)	1 (5.3)	[0.3, 22.6]	1 (4.2)	[0.2, 18.3]
Stable Disease (SD)	5 (26.3)	[11.0, 47.6]	3 (12.5)	[3.5, 29.2]
Progressive Disease (PD)	11 (57.9)	[36.8, 77.0]	18 (75.0)	[56.5, 88.5]
Not Evaluable	2 (10.5)	[1.9, 29.6]	1 (4.2)	[0.2, 18.3]

CI, confidence interval; *N*, total number of subjects; *n*, number of subjects in the indicated category; RECIST, Response Evaluation Criteria In Solid Tumors.

[a]The 2-sided 90% exact binomial confidence interval for the overall response rate was calculated using the Clopper-Pearson method.

[b]The primary endpoint of objective response rate was the proportion of subjects in the analysis population with CR or PR based on best overall RESIST v1.1 assessment any time within the active trial phase, including any unscheduled post-intervention assessments.

FPV-CV301 doses was 1 (range: 0–11). The median number of atezolizumab infusions was 3 (range: 1–30) and median duration of trial intervention was 6.1 weeks (range: 0.1–98 weeks). In Cohort 2, 79% of patients received both prime doses of MVA-BN-CV301, and the median number of boost FPV-CV301 doses was 1 (range: 0–12). The median number of atezolizumab infusions was 3 (range: 1–34) and median duration of trial intervention was 6.1 weeks (range: 0.1–101 weeks).

Toxicities

Nine patients experienced ≥ Grade 3 AEs related to treatment: 5 in Cohort 1 and 4 in Cohort 2 (Supplementary Table 4). In Cohort 1, most common AEs included fatigue (42%), decreased appetite (32%), fall (26%), acute kidney injury, anemia and diarrhea (21%, each) (Supplemental Table 5). In Cohort 1, one patient (5.3%) experienced treatment-related AE (lipase elevation) leading to intervention discontinuation. One patient in Cohort 1 died due to cardiac arrest, which was assessed as unrelated to the trial intervention. In Cohort 2, most common AEs included fatigue and injection site pain (33%, each), pyrexia (29%), injection site erythema and nausea (25%, each), back pain, cough, productive cough and decreased appetite (21%, each) (Supplemental Table 5). One patient (4.2%) in Cohort 2 experienced a treatment-related AE (pneumonitis) leading to discontinuation. High-dose steroids were used to treat toxicities in only 1 of 24 patients in Cohort 2 (4.2%) and none in Cohort 1. In general, the incidence of AEs was similar during both the priming MVA-BN-CV301 and booster FPV-CV301 periods.

Correlative studies

A significant change in CEA-specific and MUC1-specific T cells compared to baseline was not observed overall (Supplementary Fig. 1). No relationship between baseline CEA-specific T-cell level and best overall response was discerned. However, in the two patients in Cohort 2 with objective response, the geometric mean of CEA-specific T cells increased from 10.0 at baseline to 14.7 at week 52. Similarly, no relationship between baseline MUC-1-specific T-cell level and best response was discerned for either cohort. However, MUC-1-specific T cells at week 22 and week 52 were elevated compared with baseline for the three patients in Cohort 2 with SD, with means of 5.0, 16.7 and 22.0 at weeks 0, 22, and 52, respectively.

Discussion

The combination of atezolizumab with CV301, a poxvirus vaccine containing transgenes encoding tumor-associated antigens MUC1 and CEA as well as co-stimulatory molecules B7.1, ICAM-1, and LFA-3, did not demonstrate sufficient efficacy in aUC as first-line therapy in cisplatin-ineligible patients or in the platinum-refractory setting. Among 43 evaluable patients overall, objective response was observed in only three (7%) and SD (as best response) in eight (19%) patients. Consequently, the trial was halted at the interim analysis for poor efficacy. The toxicity profile was acceptable with ≥ Grade 3 AEs related to treatment in nine patients (20.9%), no treatment-related mortality and

low rates of discontinuation due to toxicities in both cohorts (5.3% and 4.2%).

Notably, a precursor vaccine, PANVAC had exhibited promising activity in multiple malignancies, especially those with limited tumor burden and minimal prior chemotherapy, in conjunction with antigen-specific T-cell immune responses [13–15]]. However, in a disappointing result, a phase III trial in metastatic castration-resistant prostate cancer, PROSTVAC, a vaccine that employed the PANVAC platform expressing prostate-specific antigen, did not extend overall survival [16].

This result in aUC is disappointing, considering that this trial combined atezolizumab with CV301, a second-generation non-replicative poxvirus vaccine based on modification of PANVAC, which employed a replicative poxvirus, to improve safety and immune response [17]. To construct CV301, a second-generation poxvirus vaccine, the amino-acid sequences in the CEA and MUC1 were modified to produce a stronger immune response with enhanced HLA binding and T-cell recognition. In a previously reported phase I trial, CV301 activated CD8 + and CD4 + T cells against MUC1 and CEA in 92% of patients in a dose-dependent fashion and demonstrated activity in colorectal cancer, a generally "cold" tumor [5]. Moreover, CV301 induced T-cell responses against brachyury, suggesting that CV301 induces antigen spreading. Interestingly, a trend in greater magnitude of MUC1-specific T-cell responses was seen in patients with somatic *KRAS* mutations compared with *KRAS* WT tumors and in less advanced disease.

This trial serves as a cautionary tale and illustrates the challenges in developing vaccines. The low response rate suggests the enrollment of patients with particularly poor prognosis. The inherent limitations include nonrandomized design, patient selection factors (median age in Cohorts 1 and 2 were 78 and 71 years, respectively) and modest sample size. There were also limited biomarker analyses in the context of early discontinuation of the trial. The sites of metastases were typical for this disease. Nevertheless, the potential biological reasons for the poor results still bear examination. The weak T-cell responses with no significant increase in post-therapy CEA- and MUC-1-specific T cells and absence of a significant overall association of immune response with objective response suggest that CV301 did not consistently generate robust anti-tumor immune response. Interestingly, responding and stable patients in Cohort 2 exhibited trends for increases in CEA- and MUC-1-specific T cells, respectively. Potentially, the pace of cancer progression did not permit the generation of a more delayed immune response. Patients were not selected for high expression of CEA or MUC1, although these antigens are commonly expressed in the vast majority of aUC tumors. First-line atezolizumab monotherapy for cisplatin-ineligible patients with PD-L1-low expressing tumors may have led to poor outcomes since subsequent trials reported an excess of early mortality in PD-L1-low tumors receiving first-line PD1/L1 inhibitors. The tumor microenvironmental mechanisms of resistance may need to be concurrently addressed, such as transforming growth factor-β and vascular endothelial growth factor [18].

A major advantage of 'off-the-shelf' vaccines is that they are more "user friendly", practical and likely to be affordable. However, their development may warrant more optimal selection of patients with earlier-stage cancer to allow longer duration of therapy and time for the generation of a potentially delayed but robust immune response, such as the perioperative or first-line maintenance settings in combination with PD1/L1 inhibition [19, 20]. Additionally, higher expression of the target on tumor cells may be necessary to yield robust immune response. Moreover, the activity may be context-dependent with greater benefit in certain molecular subgroups.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00262-022-03274-6.

Author contributions The following provided patient accrual to the trial: GPS, BLM, BAM, XXW, KLK, RJL, EYY, MTS, RBM, HHC, ACH, RJ, JSG, PG The following helped in writing the manuscript: GPS, PGThe following provided management and administrative support: CP-N, ZG, TPThe following reviewed and approved the manuscript: GPS, BLM, BAM, XXW, KLK, RJL, EYY, MTS, RBM, HHC, ACH, RJ, JSG, CP-N, ZG, TP, PG

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Declarations

Conflict of interest Guru Sonpavde: Advisory Board: BMS, Genentech, EMD Serono, Merck, Sanofi, Seattle Genetics/Astellas, Astrazeneca, Exelixis, Janssen, Bicycle Therapeutics, Pfizer, Immunomedics/Gilead, Scholar Rock, G1 Therapeutics, Eli Lilly/Loxo Oncology, Infinity Pharmaceuticals; Research Support to Institution: Sanofi, Astrazeneca, Immunomedics/Gilead, QED, Predicine, BMS; Steering committee of studies: BMS, Bavarian Nordic, Seattle Genetics, QED, G1 Therapeutics (all unpaid), and Astrazeneca, EMD Serono, Debiopharm (paid); Data safety monitoring committee: Mereo; Travel costs: BMS, Astrazeneca; Writing/Editor fees: Uptodate, Editor of Elsevier Practice Update Bladder Cancer Center of Excellence; Speaking fees: Physicians Education Resource (PER), Onclive, Research to Practice, Medscape, Cancer Network, Masters Lecture Series (MLS) Benjamin Louis Maughan: Consulting or Advisory Role: Janssen Oncology, Exelixis, Tempus, Bristol Myers Squibb, Astellas Medivation, Bayer, AVEO, Clovis Oncology, Merck, Peloton Therapeutics; Research Funding: Clovis Oncology, Bristol Myers Squibb, Bavarian Nordic, Exelixis; Travel, Accommodations, Expenses: Exelixis Bradley Alexander McGregor: Consulting or Advisory Role: Bayer, Seattle Genetics/Astellas, Exelixis, AstraZeneca, Astellas Pharma, Genentech/Roche, Nextar, Janssen Oncology, Pfizer, EMD Serono, Eisai, Dendreon, Bristol Myers Squibb; Research Funding: Bristol Myers Squibb, Exelixis, Calithera Biosciences, Seattle Genetics/Astellas Xiao X. Wei: : Advisory Board: Novartis. Research support to institution: BMS.Kerry L. Kilbridge: None Richard J. Lee: Consulting or Advisory Role - Bayer; Exelixis; Janssen Oncology; Noxopharm; Tolero Pharmaceuticals; Research Funding - Janssen Evan Y. Yu: Consult-

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